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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	R. Desai
D. BIGG et al	:	
Serial No.: 09/806,952	:	Group: 1625
Filed: April 5, 2001	:	
For: OPTICALLY...ANALOGUES	:	

600 Third Avenue
New York, N.Y. 10016
September 12, 2003

RESPONSE

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

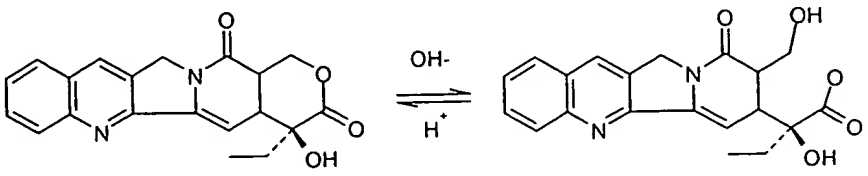
Responsive to the office action of June 27, 2003, Applicants request reconsideration of the application in view of the remarks presented herein.

The claims in the application are claims 5, 24, 26 and 27, all other claims having been cancelled.

The Examiner has maintained the rejection based upon 35 USC 102 and 103 as being obvious over the Curran et al '832 patent since Applicants have not perfected their priority. Applicants are submitting herewith an English translation of the priority document and are therefore entitled to the French filing date of February 26, 1999 which is prior to the March 2001 filing date of Curran et al. Therefore, it is deemed that this ground of rejection is obviated.

Claims 5, 24, 26 and 27 have been rejected under 35 USC 103 as being obvious over the Hauseer '727 patent taken in view of the Lavergne et al reference. The Examiner states that Applicants' compounds are homocamptothecins which are analogs of camptothecin with a 7-membered ring as compared to the 6-membered ring of Hauseer. The Examiner states that the reference teaches compounds wherein R_5 is a silicon containing group and that the references teaches that the presence of a Si containing group at that position makes them highly lipophilic. The Lavergne et al reference is cited to show that CPT and its analog hCPT show and exhibit the same properties referring specifically to page 5413. The reference, according to the Examiner, teaches that hCPT is more efficacious and concludes that the secondary reference teaches that homocamptothecins are more effective in tumor growth delay and that it would be Hauseer that the Si containing groups would make the CPT lipophilic and more effective and therefore, the claimed compounds are obvious.

Applicants respectfully traverse this ground of rejection as it is not deemed that the combination of the prior art that the Examiner has manufactured with the benefit of Applicants' disclosure would not suggest the claimed compounds to one skilled in the art. The Hauseer patent discloses lipophilic CPT derivatives. As well known to those skilled in the art, CPT shows a rapid and pH dependent hydrolysis of the lactone moiety to form an open E-ring with a hydroxy carboxylic acid function as follows:



The CPT carboxylate form (water-soluble form corresponding to the opened E-ring) is recognized by Hauseer as being less active than the lactone form. As noted in lines 11 to 18 of page 8, "The resulting CPT derivative carboxylate species will be water-soluble and have substantially reduced antineoplastic activity and...and is not the preferred form of the drug. The inventors submit that the lactone E-ring species of CPT (and its derivatives) is the preferred form of the drug for administration to subjects with cancer." Also, in lines 1 to 5 of page 9, it is stated "Since..., the carboxylate species of CPT derivatives are predicted to have lower bioavailability than CPT derivatives which have the lactone E-ring." Therefore, the inventors of the reference in an attempt to obtain active CPT derivatives with the lactone E-ring, suggested CPT derivatives with lipophilic substituents.

The introduction of a lipophilic group increases the lipophilicity of the molecule and displaces the equilibrium on the side of the closed E-ring and this displacement leads to the protection of the active lactone formed from hydrolysis. This is taught in lines 33 of page 3 through line 2 of page 4 "Further, being highly lipophilic, they can be administered in the active lactone form and will have superior bioavailability relative to water soluble CPT derivatives." This was already shown in the stabilization of the lactone moiety of CP drugs by Burke et al (Biochemistry, 1993, Vol. 32, pp. 5352-5364, a copy of which is submitted herewith).

In contrast to the CPT, the key features of the hCPT derivatives is the best stability in a slow and irreversible E-ring opening. Thus, with hCPT, there is no stability problem or equilibrium problem to solve. This can be seen from Cancer Research. Vol. 59, pp. 2939-2943, a copy of which is enclosed herewith. Thus, with these differences, the transposition of specific problems of a CPT derivative to hCPT is impossible since they are non-equivalent structures.

In order to demonstrate the non-equivalence between these two types of structures, Applicants are submitting herewith entitled Biochemistry, 1999, Vol. 38, pp. 15555-155563 which compares the CPT 6-membered ring with hCPT 7-membered rings. This study shows that the cleavage sites of the DNA by CPT and hCPT are different in their molecular environment. Therefore, one could not reasonably consider any equivalence between CPT and hCPT. All of these differences are also discussed in another publication entitled Current Pharmaceutical Design, 2002, Vol. 8, pp. 2505-2020, a copy of which is enclosed herewith. The Examiner's attention is directed particularly to the first column of page 2509 as well as the relationship between the lipophily and stability of CPT derivatives and it goes on into the second column of page 2509. For all of these reasons, one skilled in the art would not apply the teachings obtained with CPT derivatives with the structure activity relationship of hCPT derivatives. Therefore, Hauseer is not relevant to present invention and the combination of the prior art fails. Therefore, withdrawal of this ground of rejection is requested.

To illustrate the unexpected effect of the compounds of the present invention, Applicants are submitting herewith the experimental results (IC_{50}) extracted from the present invention. Compounds of Formula I_A having a silyl radical are compared to very close compounds described in the present invention without the silyl group.

Ex	R_3	R_4	R_5	IC_{50}
17	F	F	$-(CH_2)_2SiMe_3$	5,0
13	F	F	Bu	8,5
11	F	F	Phe	12
22	H	H	$-(CH_2)_2SiMe_3$	8,6
5	H	H	Bu	16
7	H	H	Phe	13

It the table, R_2 and R_5 are both hydrogen and R_1 is ethyl. It can be seen that the substitution of a butyl or phenyl group by a $-(CH_2)_2SiMe_3$ with the same substituents at the other positions increases in an unexpected way the IC_{50} which means that a substantial increase in the activity of the corresponding Si compounds. For all of these reasons, the invention was not obvious from the prior art cited by the Examiner.

In view of the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Muserlian, Lucas and Mercanti

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CAM:ds
Enclosures